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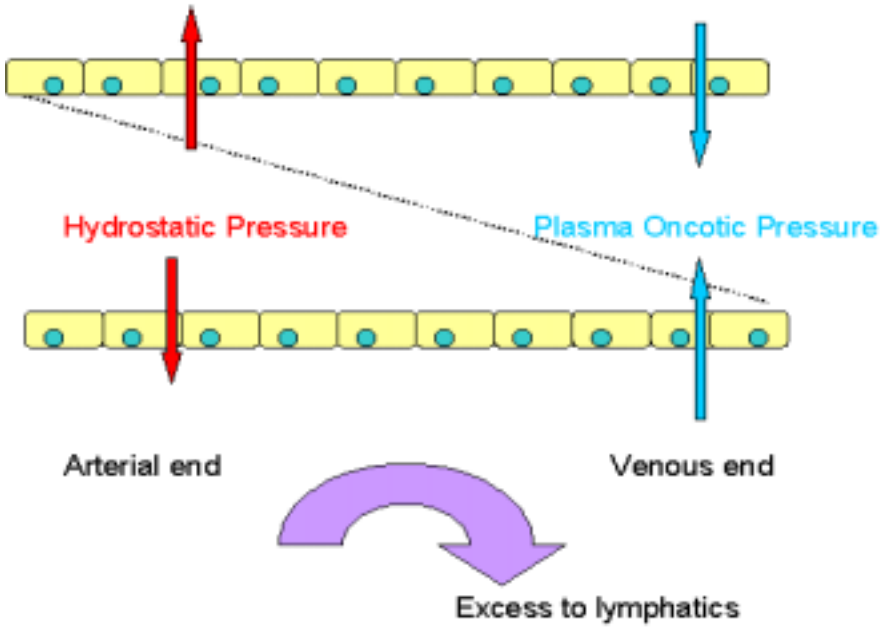
Hemodynamics – Edema

Hemodynamics, is a balance between 2 sets of opposing forces. The first is blood forcing itself through the blood vessels vs plasma oncotic pressure caused by proteins (mostly albumin) in the blood.

- Normal State: The high hydrostatic pressure in the arterioles overcomes oncotic pressure and forces fluid into the extravascular space. The hydrostatic pressure drops as the vessel turns into a venule, and the plasma proteins are concentrated as fluid leaves. In the venule, the plasma oncotic pressure overcomes the hydrostatic pressure and fluid moves back into the vessel. A small amount is left behind and is picked up by the lymphatics.



Edema

Definition: the accumulation of abnormal amounts of fluids in the interstitial spaces or body cavities. Edematous fluid is **transudate** (protein poor) or **exudate** (protein rich, containing cells). Caused by:

- Increased Hydrostatic Pressure: The pressure is so high within both the arterioles and venules that the oncotic pressure cannot move fluid back into the venules. The lymphatics cannot accommodate this fluid, so edema of tissue. Edema itself is not a disease condition—it is an indicator of an ongoing disease process.
- Decreased Oncotic Pressure: Can be caused by (1) reduced kidney function [necrosis or other causes as in diabetic nephropathy] kidney tubules leak albumin or (2) reduced liver function (hepatocytes not secreting enough serum proteins). The oncotic pressure never becomes great enough to overwhelm the venule hydrostatic pressure. Fluid is not pulled back into the venules and remains in the tissue as edema.
- Increased Permeability: Some disease states will cause the vascular endothelium to become discontinuous. Fluid will be able to leak out of the entire vascular supply causing massive systemic edema.
- Lymphatic Obstruction: The lymphatic drainage for a region is blocked by tumors or parasite. The lymphatics are not able to drain as much fluid as normal, and fluid accumulates.

Summary of causes of Edema		
Primary Cause	**Mechanism**	**Clinical Examples**
Increased Intravascular Hydrostatic Pressure	Congestive Heart Failure (heart cannot pump efficiently. Blood pools in extremities and increases hydrostatic force). Venous Obstruction (tumors, thrombi)	Systemic edema – Pitting of dependent extremities (standing up: feet and ankles, lying down: back and sacrum) Local (peripheral) edema
Reduced Plasma Oncotic Pressure	Kidney: Albuminuria Liver: Hypoalbuminemia	Systemic Edema – Pitting
Lymph Obstruction	Surgery (radical mastectomy), Tumors, Radiation, Filariasis	Localized Edema
Sodium Retention	Decreased Renal Function (Sodium restriction diets often used to reduce edema and decrease fluid load on heart)	Systemic Edema – Pitting
Increase in Capillary Permeability	Trauma, Toxins, Septic Shock, Tumors, Endothelial Tight Junction Disruption	If localized to Cerebrum: Headache, Vomiting, Loss of consciousness -- Skull cannot expand to conform to edema If localized to Lungs: Dyspnea – Inability of lungs to exchange oxygen

<u>Hyperemia/Congestion Definitions:</u>

- Hyperemia is an active process caused by dilation of arterioles to certain tissues. This is a normal physiologic or neurologic response. Examples: exercise, blushing, inflammation.
- Congestion is a passive process usually caused by obstruction of blood flow. This can be due to a failing heart that cannot pump blood fast enough—causing it to backup downstream—or due to a thrombus causing a physical obstruction of the blood vessel.

<u>Thrombosis / Coagulation</u>

Clotting and Anti-clotting are 2 opposing forces that are constantly occurring within the body. Within the clotting cascade is the mechanism that causes the clot to dissolve.

- Thrombus: A mass of platelets, fibrin, red blood cells, and white blood cells that is attached to vascular endothelia and partially obstructs the vessel.
- Clot: A mass of platelets, fibrin, red blood cells, and white blood cells that is not attached to a vessel wall.

Virchow's Triad – States the conditions leading to thrombosis.

1. Changes in the Antithrombotic Properties of the Endothelium – The endothelium normally carries anti-clotting factors. If the wall is damaged, (myocardial infarction, vasculitis, hypertension, bacterial endotoxins, or athersclerotic plaques) these factors are lost and thrombosis can occur. This is the dominant influence of thrombosis and is extremely important to thrombosis of the heart and arterial circulation.

2. Changes in Blood Flow – Normally blood flows in a laminar fashion through the vessels. The red blood cells, white blood cells, and platelets flow in the center of the vessel and the fluid flows near the edges. Turbulent flow can occur due to atherosclerotic plaques, calcification, infarction and stenosis of vessels, infections, venous valves.

   Turbulence and Stasis aid initiation of thrombosis by:
   - Disrupting laminar flow and bringing platelets into contact with the epithelium.
   - Slowing the transportation of fresh plasma to dilute activated clotting factors.
   - Slowing the transportation of plasma born clotting inhibitors.
   - Promoting endothelial activation and leukocyte adhesion.

3. Changes in Blood Composition – Clotting and anti-clotting are 2 opposing forces. If the plasma anti-clotting factors are reduced, then the balance will favor clotting. This **Hypercoagulabilit**y and can be caused by many genetic or acquired mechanisms.
    - Hypercoaglability from pregnancy
    - Diabetes
    - Post-operative
    - Cigarette smoking or oral contraceptives
    - Deficiency of clotting factors (antithrombin III, protein C, plasminogen activator)

Thrombosis vs Coagulation	
Thrombosis	**Coagulation**
Attached to the Vessel Wall	Not fixed
Requires Vessel Wall to Occur	Can Occur *in Vitro* as a result of the clotting cascade
Requires Endothelium	Does Not Require Endothelium
Involves the Adherence and Aggregation of Platelets	Does Not Require Cells

Remember that the clotting mechanisms also have anti-clotting mechanisms associated with them.

- Formation of Thrombin from Prothrombin can be lysed by Thrombomodulin.
- Formation of Fibrin from Fibrinogen can be lysed by Plasmin.
- Plasminogen Activator Inhibitors block the activation of Plasminogen to Plasmin (a pro-clotting effect).

Fates of a thrombus

- Anti-clotting factors dissolve the thrombus. Cannot tell how many thrombi form and dissolve every day since they are only detected when they become pathological
- Thrombus Re-canalization. Partial lysis of the thrombus results in small holes. Endothelial cells can form and cover these holes and partial blood flow can be re-established.
- The thrombus can become organized into the wall of the blood vessel. A layer of endothelial cells proliferates over the thrombus and you are left with a lump in the side of the vessel. This causes a partial obstruction of the vessel and may cause turbulent blood flow.

Remember, Virchow's Triad says that turbulent blood flow can lead to further thrombus formation.

- Venous Thrombosis is often caused by sluggish blood flow in the veins (due to lack of exercise and movement), a serious complications of surgery in elderly patients. Platelets aggregation occurs in areas of stasis (sluggish venous blood flow) or turbulence (around venous valves) followed by deposition of fibrin.
- The thrombus grows in the direction of blood flow (towards the heart) and may break loose.
- They move through the heart and into the lungs where they form an embolus. Sometimes the entire thrombus detaches (called a "Saddle Embolus") and travels up to the heart. A saddle embolus can get trapped in a pulmonary artery and occlude the entire blood flow to that lung.

<u>Embolism</u>

Definition: a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a different site than its point of origin. The embolus becomes lodged in a small blood vessel, occluding blood flow and causing infarction. Most emboli are derived from thrombi but rare versions can arise from amniotic fluid, bone or bone marrow fragments (after a crushing injury), tumors, or air and nitrogen bubbles.

An Air Embolism occurs commonly when divers dive low enough, increasing water pressure dissolving air (which is mostly nitrogen) into the blood (similar to how pressure is applied to soft drinks in order to dissolve carbon dioxide). If they resurface too quickly the pressure is released. The dissolved gasses bubble out of the blood (analogous to opening a can of Pepsi) and the bubbles can become caught in vessels. This phenomenon is called "The Bends" or decompression sickness and usually results in joint pain. Occasionally, an air embolus can travel to the brain and cause a cerebral embolism. This is a special for you Navy folks.

An Amniotic Fluid Embolism is a very rare occurrence of a normal pregnancy. Rupture of the amniotic sac leads to leakage of amniotic fluid into the placental vessels. Amniotic Fluid is very thrombogenic and can lead to Disseminated Intravascular Coagulation (DIC)—a situation where all the clotting mechanisms are turned on at once and blood starts clotting in situ.

Tumor Emboli arise from malignancies that have invaded blood vessels and break away.

An **Arterial Embolism** (also called systemic embolism) is usually caused by a thrombus derived from the left ventricle or the left atrium (e.g. vegetations on the cardiac valves, or from thrombi occurring around areas of myocardial infarction). Paradoxical Emboli—an embolus that originates in the venous system but bypasses the lungs via a patent foramen ovale or ductus arteriosus to enter the arterial system. Arterial emboli almost always lead to **infarction** since the embolus will almost always become lodged in a capillary. Infected emboli from cardiac valve vegetation give rise to a septic condition—especially dangerous when occurring in the brain. The most likely organs injured by arterial emboli are the brain, lower extremities, spleen, and kidneys.

A **Venous Embolism** usually arises from deep veins of the lower extremities such as the deep pelvic or iliac veins. The **Pulmonary Embolism** is the most common and most lethal variety of embolus. Small emboli resolve automatically. The lung has enough collateral blood supply and excess capacity that the embolism is asymptomatic. Multiple emboli can cause chronic pulmonary hypertension. The most serious kind of pulmonary embolism is caused by **saddle embolus,** which occurs in patients who are bedridden for extended periods of time. Sluggish venous blood flow and thrombi formation in the deep leg veins lead to emboli when the thrombus breaks off and flows through the heart to block blood flow to the lung. Blocking the pulmonary artery results in loss of returning blood flow to the left side of the heart, myogenic shock, and death.

Infarction

Definition: a localized area of ischemic necrosis in an organ or tissue resulting from occlusion of either its arterial supply or venous drainage. Infarction can occur in several ways:

- Thrombosis – A large thrombus totally occludes a blood vessel.
- Embolism – An embolus gets lodged in a small vessel and occludes blood flow.
- Compression – A tumor or scar tissue can compress a blood vessel and occlude blood flow.
- Twisting – A blood vessel is twisted which occludes the blood flow through it.
- Atherosclerosis – Atherosclerotic plaques build up and gradually occlude blood flow.

Evolution of the Infarct

- Few Hours: Tissue is slightly darker but ill-defined
- 24 Hours: Intense color change observed with well-defined margins.
- Several Days: Necrosis and inflammation occurs. The tissue will be digested by tissue macrophages and replaced with scar tissue.

White Infarcts: solid organs with a single blood supply and are usually due to an arterial embolism. There may be a transient hemorrhage present but they become pale within about 24 hours. White infarcts occur most commonly in the heart, kidneys, and spleen.

Red Infarcts: loose tissues with a double circulation and are caused by venous occlusion. The occlusion causes necrosis of tissue, but the dual blood supply allows blood to leak into the

necrotic area. The red blood cells cause the infarcted area to become red. Red infarcts can also occur in tissues that were previously congested before the infarction.

The extent of tissue damage from an infarct depends on:

- General status of the blood and cardiovascular system
- The anatomic pattern of the blood supply. If collateral blood circulation can take over for most of the ischemic tissue, the infarct will likely not be fatal.
- Rate of development of the occlusion of the blood supply. A slow developing occlusion can be compensated for by angiogenesis (creation of collateral blood supplies). A fast developing occlusion (such as a saddle embolus) is much more serious.
- Vulnerability of the tissue to ischemia. The brain is absolutely dependent on the blood supply and cannot tolerate ischemia. Unfortunately, the brain is also of utmost important for our continuing existance. The fingertip can tolerate much larger bouts of ischemia and is relatively unimportant in the grand scheme of things.
- Activity of the tissue. The bowel is very metabolically active. A bowel infarction is very serious because the necrotic tissue will allow the bowel contents to leak. Bacteria within the bowels will then cause septic shock—a very serious condition.

<u>Shock</u>

Definition: a state in which the supply of blood to tissue is inadequate to meet the metabolic demands of that tissue. Shock results from assaults leading to hemodynamic or vascular collapse. Shock depends very much on the rate of onset of the vascular changes as well as the general health of the person experiencing shock.

Symptoms of Shock

- Hypotension – Caused by loss of blood from hemorrhagic shock or reduced vascular tone (which occurs in septic shock)
- Oliguria – Kidney function is one of the major indicators of shock. The loss of renal perfusion is going to lead to renal shutdown.
- Weak, Rapid Pulse
- Tachycardia
- Cold, Clammy Skin
- Changes in Respiration or Sensorium
- Pallor or Cyanosis

Types of Shock

- Cardiogenic Shock – Failure of the heart to pump. Can be caused by an infarct, a saddle emboli blocking blood from returning to the heart, and many others:
    - Mechanical Restrictions: Valvular disease, tamponade (bleeding into the pericardial sack; the blood prevents the heart from expanding), tumors, thrombi on the wall of the heart.
    - Myocardial Insufficiency: Cardiomyopathies, increased plasma K+(usually due to renal insufficiency), toxins, infarction, arrythmia.
    - Impaired Venous Return: Septic or anaphylactic shock, tension pneumothorax, pulmonary embolism.
- Hypovolemic Shock – Fluid loss by hemorrhage, vomiting, diarrhea (Cholera), burns.
- Septic Shock – Can be caused by bowel infarction. Leads to endothelial damage and DIC.
- Neurogenic Shock – Can be caused by anesthesia, spinal cord injury, or severe pain.
- Anaphylactic Shock – Type I hypersensitivity reaction mediated by IgE. Occurs during severe allergic reactions and causes severe vascular permeability.

<u>Hemorrhage</u>

Definition: a discharge of blood from vascular to exterior compartments. Caused by vessel injury (scapel, trauma, cancer, aneurysm, clotting conditions). Consider location of hemorrhage: skin vs brain.

- Very small hemorrhages (1-2 mm): Petechiae
- Slightly larger hemorrhages (3 mm): Purpura
- Large subcutaneous hemorrhages (> 1-2 cm): Ecchymoses (bruises)
- Large accumulations of blood in a body cavity: Hemothorax, hemopericardium, hemoperitoneum, hemoarthrosis.

Septic Shock
Definition: Collapse of the circulation due to infection with (usually) Gram-negative organisms; also anthrax lethal factor. LPS liberated from bacteria activates the cytokine cascade and clotting factors. This results in DIC, circulatory collapse and multiple organ failure.
Disseminated Intravascular Coagulation (DIC)
Definition: a complex clotting disorder caused by imbalance of clotting and anti-clotting factors, resulting in formation of numerous microthrombi in the microcirculation. This is most likely cytokine driven or caused by a change in the endothelium induced by cytokines.

There are 3 stages of shocks
Phase 1: Cardiac output and blood pressure maintained by tachycardia and peripheral vasoconstriction. Sodium retention in the kidney maintains body fluid volume.
Phase 2: Tissue hypoperfusion leading to hypoxia, anaerobic glycolysis, and cellular acidosis. Brain and kidney damage (tubular necrosis). Patients may recover from Phase 2 Shock with medical support.
Phase 3: Severe and irreversible tissue damage. Heart failure damaged pancreas releases Myocardial Depressant Factor (MDF) that further reduces cardiac performance. Acute tubular necrosis gastrointestinal hypoperfusion leads to leakage of bacteria and LPS and septic shock.

Complications of Shock:
- Fever, brain death
- Adult respiratory distress syndrome (ARDS)
- Focal necrosis of liver, myocardium, kidney, intestine
- Splenic congestion
- Vasodilation and splanchnic pooling